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ASSISTANT GENERAL COUNSEL
BAXTER INTERNATIONAL INC.
LAW DEPARTMENT
ONE BAXTER PARKWAY, DF2-2E
DEERFIELD, IL 60015

EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/964,273	BRYNJELSEN ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 12-19-07 is acknowledged.

Claims included in the prosecution are 1-19 and 21-38.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 8, 9, 11, 17, 18, 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

According to the parent claim 7, the compound is a surface active agent. The dependent claims 8 and 9 recite polysaccharides and various celluloses. It is unclear as to how these compounds can be considered as surfactants. Similar is the case with claims 17 and 18.

'other proteins' in claim 11 and 'other high shear conditions' in claim 23 are indefinite expressions; the examiner suggests reciting specific proteins and specific conditions in these claims.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-7, 11 and 21-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al (5,916,596) as set forth in the previous action.

5. Claims 1-9, 11 and 21-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al (5,916,596) in view of Popescu (5,009,819).

The teachings of Desai have been discussed before. What is lacking in Desai is the sonication below the room temperature.

Popescu discloses the preparation of submicron size particles of chloroquine. The process involves emulsification of phosphatidylcholine in diethyl ether/chloroform and aqueous chloroquine solution and sonicating the mixture at a temperature of 18 to 20 degrees (example 1).

Sonicating the mixture of Desai at a temperature of 18 to 20 degrees would have been obvious to one of ordinary skill in the art with the expectation of obtaining the best possible results since the reference of Popescu shows that the sonication process could be practiced below the room temperature.

6. Claims 1-9, 11, 21-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al. US 5916596 in view of Popescu US 6090406 as set forth in the previous action.

Applicant's arguments to the above two rejections (Desai or Desai in view of Popescu (6,090,406) have been fully considered, but are not found to be persuasive. Applicant argues that US 2003/0096013 which is cited is not available as a reference against pending claims. In response, the examiner points out that this reference is only cited as interest and not as reference over which the claims are rejected. Applicant cites the American heritage Dictionary to show that the room temperature to be an indoor temperature of from 20 to 25 degrees C and argues that at a temperature below room temperature limitation recited in all pending claims is entitled to and should be accorded patentable weight. That might be true. However, applicant has not shown any unexpected results by conducting the evaporation below the room temperature. As pointed out before, it would have been obvious to one of ordinary skill in the art to use suitable temperatures depending upon the compound's ability to withstand any particular temperature. As the reference of Orsolini (5,637,568) submitted by applicant indicates that some organic solvents are volatile and solvents such as methylene chloride evaporate spontaneously during agitation (col. 3, lines 17-26). From this fact coupled with the fact that sonicators by themselves remove organic solvents, one of ordinary skill in the art would be motivated to use a suitable temperature, a temperature which is below the room temperature if necessary, if the active agent is susceptible to higher temperatures. The examiner has already the reference of Caza (6,079,508) to show that there are some ultrasonic processors, which remove the solvent (see col. 6, lines 9-17). The examiner has also cited Werling (2003/0096013) which shows sonication removes solvent (0059). As also pointed out before, instant claim language

'comprising' does not exclude other evaporation conditions carried out simultaneously and the examiner cited the references of Janoff and Popescu (5,009,819), which teach concurrent evaporation by Nitrogen while sonicating the emulsion of interest (col. 31,lines 25-30 of Janoff; Example 1 of Popescu). Finally, the examiner points out that applicant has not shown any criticality of performing the sonication step to remove the solvent below the room temperature since on page 8, lines 10-12 of the specification, applicants themselves state that any residual solvent that exists may be removed by means such as evaporation by the addition of heat. Applicant argues that Desai makes it clear that sonication is not used to achieve evaporation as claimed and points out to col. 7, lines 52-54 of Desai. This argument is not persuasive since as recognized by applicants themselves, Desai's teachings at this location are 'optional' and not critical. Similarly, applicant's arguments that Popescu does not remedy this deficiency since Popescu discloses sonicating a solution at elevated temperature to remove substantially all ether therein are not persuasive. The boiling point of methylene chloride is 39.75 (see Merck Index, page 5941) and according to Orsolini' teachings discussed above, this compound evaporates spontaneously during agitation itself. According to Merck Index, ether has a boiling point (34.6) which is much less than methylene chloride and therefore, it would have been obvious to one of ordinary skill in the art that this compound evaporates faster than methylene chloride discussed by Orsolini. As discussed above, if the active agent is heat sensitive, one of ordinary skill in the art would select a temperature, which is less than room temperature, if the active agent is heat sensitive, since this solvent evaporates faster than even methylene chloride.

Applicant's arguments that Popescu only sonicates solutions and not emulsions are not persuasive since Popescu is cited to show that sonication step to remove organic solvents is known in the art and the principle of solvent removal by sonication would be the same whether the organic solvent is present in a system by itself or in the form of an emulsion.

7. Claims 1-9, 11, 21-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al. US 5916596 in view of Popescu US 6090406 as set forth in the previous action, further in view of Popescu (5,009,819).

The teachings of Desai and Popescu (406) have been discussed before. Briefly, Desai teaches the emulsification process using sonication technique to prepare nanoparticulate suspension. Desai however, does not teach that the sonication process is used to remove the organic solvent.

Popescu (406) teaches that the sonication process can be used to remove organic solvent (Example 1). The temperature at which the sonication is carried out however, is above the room temperature.

Popescu discloses the preparation of submicron size particles of chloroquine. The process involves emulsification of phosphatidylcholine in diethyl ether/chloroform and aqueous chloroquine solution and sonicating the mixture at a temperature of 18 to 20 degrees (example 1).

The use of the sonication to remove the solvent would have been obvious to one of ordinary skill in the art since the reference of Popescu (406) shows that the removal of a solvent by sonication is a routine practice in the art. Sonicating the mixture of Desai

at a temperature of 18 to 20 degrees would have been obvious to one of ordinary skill in the art with the expectation of obtaining the best possible results since the reference of Popescu (819) shows that the sonication process could be practiced at a temperature of 18 to 20 degrees.

8. Claims 1-19 and 21-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Violanto (4,826,689) in combination with Parikh (5,922,355) and Caza (6,079,508) of record.

Violanto teaches a method of preparing submicronized particles formed by precipitation of the water insoluble compound into an aqueous solution from organic solution (col. 4, lines 32-37). The particle size is in the range 0.5-1.5 microns (col. 3, line 41). The organic solvent to non-solvent liquid ratio is 1:100 to 100:1 (col. 3, lines 54-56). The reference further teaches using surfactants such as poloxamer, and suggests that any other surfactant known to those of ordinary skill would be suitable (col. 6, lines 50-55). The reference teaches that the mixture is stirred (col. 5, line 21, col. 6, lines 56-60). What is lacking in Violanto is the teaching of sonicating the mixture at a temperature below room temperature and the removal of the organic solvent.

Parikh discloses a method of preparing submicronized particles of poorly water soluble pharmaceutically active agents comprising reducing the particle size through sonication, homogenization, milling, micro fluidization and precipitation or recrystallization and precipitation of the compound using antisolvent and solvent precipitation techniques (col. 10, lines 23-29). The steps of the method comprise mixing the water insoluble pharmaceutically active ingredient, a phospholipid, with at least one

nonionic, anionic, or cationic surfactant and sonicating the mixture at a temperature of 18 degrees (Example 1, col. 10, lines 30-34). Suitable surface-active modifiers used in the invention are listed in column 3, lines 6-30). Parikh's teaches sonication the composition mixture (col. 4, lines 50-56). A suspension of the particles was made in water (col. 5, 2-3). The particles sizes of the particles were in the range 337-361 nm (col. 5, lines 10-22). Parikh lists types of water insoluble pharmaceutical compounds that would be suitable for this invention (col. 2, lines 52-64). The number weighted particle size range is 63-76 nm (col. 5, lines 20-22).

The use of a sonicator in the process of Violanto would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since the use of Violanto for the preparation of submicronized particles of active agents is known in the art as evident from Parikh. Since Violanto teaches a wide range of organic solvent: non-solvent ratios and if the organic solvent is in excess, it would have been obvious to one of ordinary skill in the art to use the sonicator to remove the solvent to such levels as to form the precipitation of the active agent since the reference of Caza teaches that solvents can be removed by sonication (col. 6, lines 9-18).

9. Claims 1-19 and 21-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Violanto (4,826,689) in combination with Parikh (5,922,355), further in view of Popescu (6,090,406) as set forth in the previous action

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the rejection over the combination is not well understood since Violanto introduces a precipitating liquid into an organic solvent

containing a dissolved organic compound in order to form particles and that the reference does not disclose an evaporation step. This argument is not persuasive since violanto's process clearly depends on the reduction of the solubility of the compound in organic solvent by the addition of non-solvent and Violanto clearly teaches the separation of the organic solvent (abstract). Violanto further teaches that depending on the organic compound and desired particle sizes, the parameters of temperature, ratio of non-solvent to organic solvent, infusion rate, stir rate and the volume can be varied (abstract). In essence, it would have been obvious to one of ordinary skill in the art that if the organic solvent amount is greater, either the non-solvent amounts have to be increased or the organic solvent amount has to be decreased in order to precipitate out the compound. Since sonication is known to decrease the amount of organic solvent by the evaporation of the organic solvent, such a step would have been obvious to one of ordinary skill in the art.

Applicant argues that Parekh adds nothing further and like Violanto, Parikh fails to disclose or suggest the evaporation step; According to applicant, the fact that some solvent likely evaporates when the mixture of Example 1 is sonicated is irrelevant and that Parikh like other cited references, fails to disclose or suggest evaporating essentially all of the water immiscible organic solvent by sonicating the system/emulsion at a temperature below room temperature. These arguments are not persuasive. First of all, Parikh teaches sonication at 18 degrees (below room temperature). Secondly, the purpose of adding non-solvent is to precipitate the active compound and as noted from Popescu, sonication step removes the organic solvent if it is excess and applicant has

not shown any criticality of removal essentially all of the organic solvent by sonication instead of other steps taught by prior art. Applicant's arguments that the teachings of Parikh are applicable to solutions and not multiphase emulsions are not persuasive since Example 1 of Parikh shows the lipid phase (phosphatidylcholine) and aqueous phase (water).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1612

GSK